

Aus der Dermatologischen Klinik und Poliklinik
der Universität Erlangen-Nürnberg
Direktor: Professor Dr. med. O. Hornstein

Erlanger Studie über 104 lymphonodektomierte Melanompatienten der Jahre 1967 bis 1974

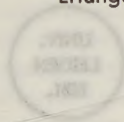
**Inaugural-Dissertation
zur Erlangung der Doktorwürde
dem Fachbereich Medizin
der Friedrich-Alexander-Universität
Erlangen-Nürnberg**

vorgelegt
von
Gerhard Aloisius Wutz
aus
Regensburg

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Early Metastases in Regional Lymph Nodes and Prognosis of Malignant Melanoma

Histological and Clinical Examinations in 104 Lymphadenectomized Patients*

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Summary. In 104 malignant melanoma patients who underwent lymphadenectomy (67 females, 37 males), correlations were studied between histologically diagnosed lymph node metastasis, the type of malignant melanoma and the depth of invasion according to Clark, as well as other parameters. In 35.6% of the patients, metastases of the primary tumor were found in one or several regional lymph nodes. In about one third of the patients, the clinical and histological lymph node findings were proven to diverge.

The female: male ratio of generally about 2:1 shifted to 1:1 in the group of patients with lymph node metastasis, i. e. cases with lymph node metastasis were found significantly increased in the male sex, and also, when primary tumors were localized on the trunk. A prognostic correlation between the two parameters, sex and localization, is suggested by the high incidence of histologically diagnosed metastases in 1 or 2 lymph node regions, when malignant melanomas were localized on the trunk in males. As to the types and the micro-stages of primary tumors, the number of cases collected until now does not permit establishing clear correlations with the incidence of lymph node involvement.

Calculating the 5-year-survival rates for patients with and without lymph node metastasis according to the "actuarial method", we found the prognosis to depend largely on the presence or absence of lymph node involvement, even at a time as early as at primary tumor excision. Our results support the indication for prophylactic lymphadenectomy in malignant melanoma, provided the primary tumor has reached or surpassed the micro-stage 3.

Zusammenfassung. Bei 104 lymphadenektomierten Melanom-Patienten (67 Frauen, 37 Männern) wurden die möglichen Beziehungen zwischen histologisch nachgewiesenen regionären Lymphknotenmetastasen und dem Typ, der Invasionstiefe des Primärtumors sowie anderen Parametern untersucht. In 35,6% der Fälle wurden Metastasen in einem oder mehreren Lymphknoten entdeckt. Bei jedem 3. Patienten stimmten der klinische und histologische Lymphknotenbefund nicht überein.

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Die Relation Frauen:Männer von etwa 2:1 veränderte sich bei den Fällen mit regionalen Lymphknotenmetastasen in 1:1, d.h. diese waren bei Männern signifikant bevorzugt. Angesichts der nach unseren Untersuchungen hohen Quote von Lymphknotenmetastasen bei Männern mit malignem Melanom am Rumpf stellt der Lymphknotenbefall ein wesentliches prognostisches Bindeglied zu den Parametern „Geschlecht“ und „Lokalisation“ dar. Hinsichtlich des Typs und der Invasionstiefe primärer maligner Melanome erlaubt die bisher erreichte Patientenzahl noch keine endgültige Aussage in bezug auf die Häufigkeit der lymphogenen Metastasierung.

Die nach der „actuarial method“ berechneten 5-Jahres-Überlebensraten unserer Patienten zeigen eine deutliche prognostische Abhängigkeit von regionalen Lymphknotenmetastasen, wenn diese bereits zum Zeitpunkt der Erstoperation vorhanden sind. Unsere Ergebnisse rechtfertigen die Indikation zur prophylaktischen Lymphadenektomie beim malignen Melanom, wenn eine Mindestinvasionstiefe des Mikrostadiums 3 vorliegt.

1. Introduction

The prognosis of malignant melanoma depends on various parameters, such as the type of development and the localization of the primary tumor, the priority of horizontal or vertical growth as well as the patient's age and sex [8, 15, 20, 21, 30]. These parameters essentially influence the classification of malignant melanomas.

Since the beginning of this century, a distinction was made between primary “nodular melanoma” (NM) and “lentigo maligna melanoma” (LMM), the latter arising in lesions of Dubreuilh's “lentigo maligna” (Hutchinson's melanotic freckle) [5, 13]. In recent years, “superficial spreading melanoma” (SSM) as an other type of malignant melanoma, has been distinguished [4, 16, 17, 19, 23, 31]. Hence, at least three varieties of malignant melanoma can be identified, particularly on the basis of differing rates of horizontal and vertical growth [15].

Besides structural differences of the primary tumor, the depth of invasion and the occurrence of regional lymph node metastasis are regarded as important criteria for prognosis. Definite prognostic differences are found statistically between the types of malignant melanoma, in so far as “nodular melanoma” has the most unfavourable outcome and “lentigo maligna melanoma” a somewhat better one.

The maximum depth of invasion reached by the time of surgical treatment is histologically defined in terms of “micro-stages” [2, 4, 10, 14, 23, 31, 34]. The prognosis gets worse as invasion increases [2, 4, 10, 14, 23, 31, 34].

With regard to lymph node metastasis, prognosis becomes remarkably poor when the nodes are found enlarged on palpation, i.e. in *clinical stage II* [20, 21, 24, 29, 33]. On the other hand, the classification into *pathological stages*¹ [3, 6, 7, 21, 24, 28, 31] is based on the historical recovery of lymph node metastases after surgical removal not only of palpable lymph nodes (“therapeutic” lymphadenectomy), but of insuspicious ones as well (“prophylactic” or “elective” lymphadenectomy).

¹ Abbreviated as *patho-stages*

There have been quite a number of publications on the subject of regional lymph node dissection as a predetermined measure in the therapy of malignant melanoma [1, 3, 6, 7, 21, 24, 28, 31]. But, to our knowledge, there is a lack of prospective papers dealing with the systematic histological evaluation of lymph nodes, and correlations have not been studied as yet between the patho-stages and the modern classification of malignant melanomas, including the type of melanoma and its depth of invasion.

With regard to our melanoma patients who underwent regional lymphadenectomy in Erlangen since 1967, the following questions will be considered:

- Are there any relations between the occurrence of lymph node metastasis and the type and depth of invasion of the primary tumor?
- Does lymph node metastasis also depend on non-histological features?
- Are there differences in the survival rate in cases of patho-stage I and II?

2. Clinical and Histological Examinations

From 1967 until the end of 1974, 212 patients with primary, untreated malignant melanoma were examined; the cases were documented according to the guide-lines advised by the study group "Malignes Melanom" supported by the Deutsche Forschungsgemeinschaft. This number of patients includes only cases in which the diagnosis was histologically confirmed.

2.1. Therapy

In 104 patients, the primary tumor was widely excised 1–2 h after one single irradiation (6000–8000 R, Dermopan Siemens, stage III or IV), and the regional lymph nodes were completely dissected afterwards [11, 12]. As a rule, lymphadenectomy was combined with tumor excision. In 16 cases it was done after an average interval of 2 weeks (ranging from 1 to 4 weeks).

According to the localization of primary tumor, the cervical, axillary or groin lymph nodes (including the iliac and aortal nodes) were removed. Block dissection (including the skin bridge between the primary tumor and the regional lymph nodes) was performed in 30 cases.

Regional lymphadenectomy was omitted

- in microstage 2 of malignant melanoma,
- when the tumor was localized around the middle of the trunk, hence, the removal of more than 2 lymph node regions would have been required,
- when patients were over 75 years old, or in poor general health,
- when refused by the patient.

2.2. Histotechnical Preparation

After formaldehyde fixation of the bulk of tissue, each lymph node was carefully prepared. Paraffin sections of 5 μ were stained with H.-E. All slides were systematically evaluated by one of the authors (F. W.). Since 1972, in cases of negative histological findings, each lymph node was cut at levels of 200 μ into serial sections of 5 μ .

2.3. Histological Typing of Malignant Melanomas

The histological slides of all malignant melanomas from our patients who underwent lymphadenectomy were examined independently by two of the authors. The results were discussed and then

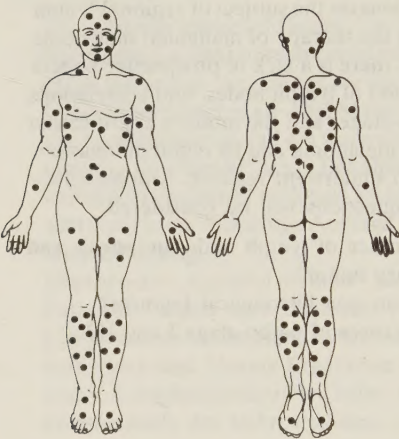


Fig. 1

brought to a consensus. In 12% of the primary malignant melanomas, there were both the characteristics of SSM and LMM. In order to classify these cases, clinical aspects were also taken into account. (A paper on this issue is being prepared.) When the primary lesion had a vertical diameter of more than 0.76 mm [2], it was generally graded into micro-stage 4 or 5 according to Clark's classification. A possibly ensuing shift from micro-stage 3 to 4 did not influence the indication for lymphadenectomy.

2.4. Patients.

Out of 104 patients with malignant melanoma who underwent lymph node dissection, 67 were female, and 37 male.

As Figure 1 shows, malignant melanomas were situated most frequently on the legs (45 cases: 35f, 10 m). In 38 cases, the tumor was localized on the trunk (16f, 22 m), in 11 cases on the arms (9f, 2m) and in 10 cases in the head and neck region (7f, 3m).

The surviving patients have been observed for different periods of time. 34 patients (16f, 18m) had died after an average time of 23.4 months after the first treatment. The remaining 64 patients (46f, 18m) are free of clinical symptoms and are now under observation for an average time of 35.8 months.

To obtain an over-all assessment of prognosis in our patients, the uncorrected, cumulative survival rates were calculated according to the "actuarial method" published by the UICC [32]. This method allows for cases in which the post-operative observation period has yet been too short for evaluation by the direct statistical method [31].

3. Results

3.1. Clinical and Histological Lymph Node Findings

Regarding the clinical and the histological lymph node findings in our patients, the following distribution was obtained:

Clinical stage I 82	Pathological stage I 67
Clinical stage II 22	Pathological stage II 37

		Histology	
		+	Ø
Palpation	Ø	25	57
	+	12	10
Incongruous:		35 = 33.7%	

Fig. 2. Clinical and histological lymph node findings

82 patients (78.8%) ranged under the clinical stage I (showing no palpable lymph node enlargement) and 22 patients (21.2%) under the clinical stage II (with suspicious lymph node enlargement), whereas 67 patients (64.4%) were in the patho-stage I (no evidence of lymph node metastasis) and 37 (35.6%) patients in the patho-stage II (lymph node macro- or micro-metastases diagnosed by histology).

In 35 of 37 patients in patho-stage II, tumor involvement of 1 or more lymph nodes was proven without additional sections. In only 2 cases the histological examinations was "negative" at first, whereas after serially sectioning at 200 μ levels, melanoma cells were discovered. In 9 cases there were only lymph node micro-metastases (term defined in 35). When mainly the superficial lymph nodes of the groin area showed tumor cells, profound lymph nodes were not affected, except for 1 case showing involvement of several iliac and aortal nodes. On the other hand, there was no metastasis into profound lymph nodes without involvement of any superficial ones. 25 out of the 37 patients in patho-stage II had clinically inapparent lymph node metastases which were demonstrated by histology; few of them had only micro-metastases.

As Figure 2 demonstrates, the clinical and histological findings do not correspond in 33.7% of our cases. Among the 22 cases with clinically established lymph node enlargement, 10 (= 45%) did not show any tumor cells. This percentage exceeds that of patients with clinically inconspicuous but histologically positive lymph nodes (25 out of 82 cases = 30.5%). In other terms, a clinically suspected stage II could not be verified histologically in nearly every second case, while a clinical stage I was not consistent with the histological lymph node involvement in at least 1 case out of 3. It should be considered, however, that the impression obtained by the palpation of lymph nodes may depend on subjective and other criteria such as a patient's adiposity, whereas the histological examination yields objective and definite results.

3.3. Type of Malignant Melanoma and Depth of Invasion

With respect to the general distribution of different types of malignant melanoma (Fig. 3, on the upper right), the percentage of LMM (15.4%) in our cases corresponds with the data presented by other authors [4, 18], while SSM (37.5%) appears under-represented as compared with NM (47.1%). This may be partly due to selection, as lymphadenectomy was indicated more often in cases of NM than in cases of SSM. Regarding the levels of invasion (Fig. 3, right lower corner), there is some difference between our data and those published so far [2, 4, 19, 34]. A decreased percentage

Cases with
Lymph Node Metastases
($n = 37$):

Total Group ($n = 104$):

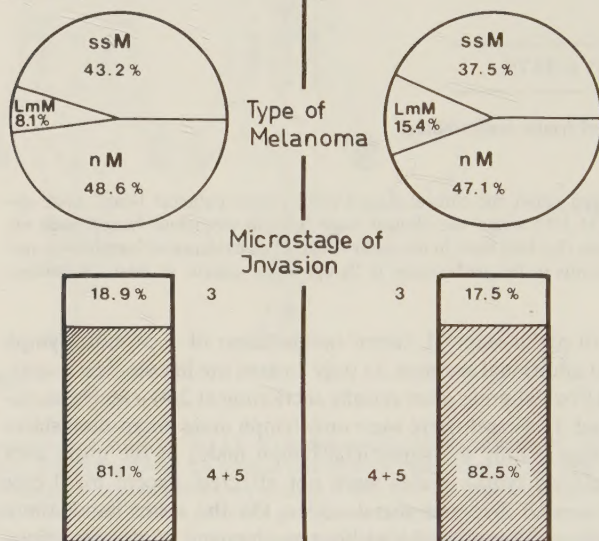


Fig. 3. Lymph node metastasis in relation to type of melanoma and microstage of invasion

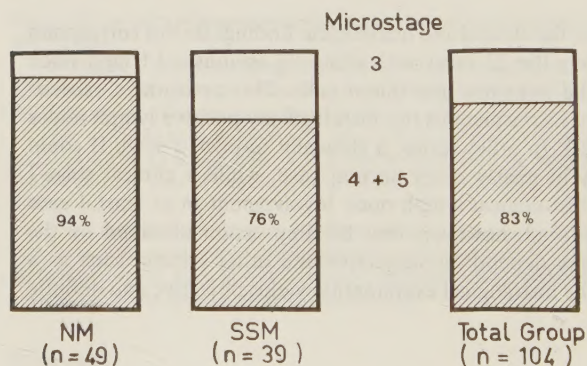


Fig. 4. Levels of invasion related to type of melanoma

of micro-stage 3 (17.5%) and an increase in micro-stages 4 and 5 (together 82.5%) was noted.

The relationship between the type of melanoma and the depth of invasion is outlined in Figure 4. The micro-stages 4 and 5—represented by the hatched areas—are shown to predominate significantly in NM as compared with SSM ($p < 0.05$), which agrees with the results of other authors [4, 18].

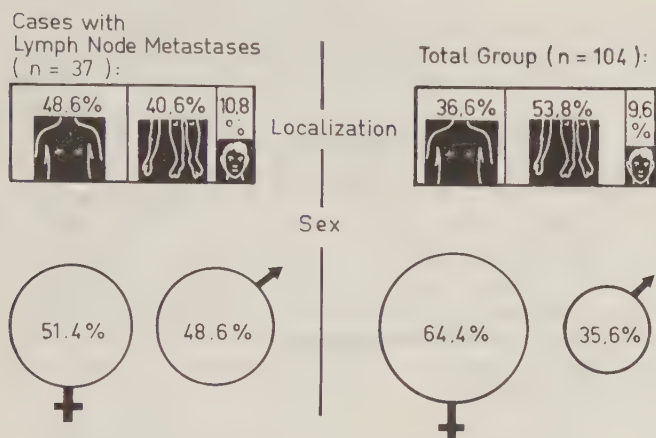


Fig. 5. Localization of melanoma, sex and lymph node metastasis

3.3. Type of Malignant Melanoma and Depth of Invasion as Related to Lymph Node Involvement

The distribution of types malignant melanoma and depths of invasion found in cases with lymph node metastasis does not differ significantly from the general one (Fig. 3).

In the group of patients with lymph node involvement, the number of cases of SSM was found rather increased, while that of LMM was reduced – both compared to the total group. However, the rather small number of patients followed-up until now does not permit establishing statistical correlations between the type of melanoma and regional lymph node metastasis.

Regardless of the type of melanoma, we were unable to find a significant correlation between the depth of invasion of the primary tumor and the incidence of lymph node metastasis, as the distribution of micro-stages did not deviate notably from that in the total group.

When the vertical diameters of melanomas were measured, no difference was recognized between the group with lymph node involvement and the one without. The medium diameter of the tumors in each group was 3 mm.

3.4. Localization of Malignant Melanomas, Sex and Regional Metastasis

As the prognosis of malignant melanoma in males and in sites on the trunk is regarded as being poor [8, 20, 21, 24, 26, 29], the incidence of lymph node involvement was analysed as to the patient's sex and the localization of primary tumors. Both categories were found to be correlated with an increased rate of lymph node metastasis (Fig. 5), which proved to be significant. However, it should be taken into account that in 15 out of 18 cases with malignant melanomas on the trunk, two lymph node regions (both axillae or one axilla and one groin) were dissected, hence the probability to detect metastases may have risen. Among 19 patients (15 with melanomas on the trunk, 4 on other sites), who underwent biregional dissection, 10 (52.6%) had

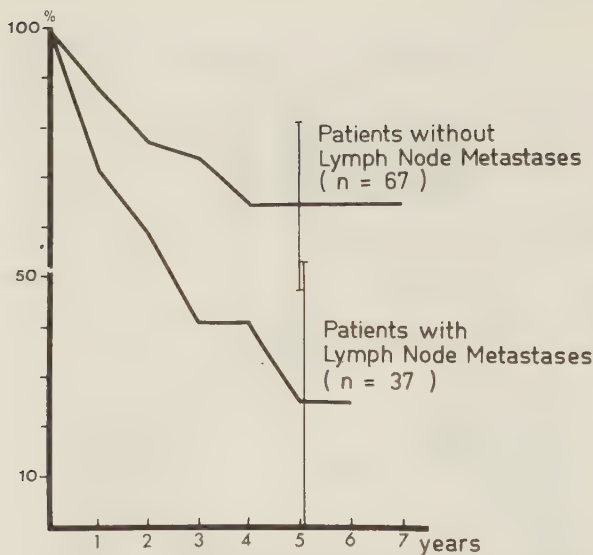


Fig. 6. 104 lymphadenectomized melanoma patients. Survival curves established by the "actuarial method"

metastases, while the same was true for only 27 out of 85 cases with one-regional lymphadenectomy (31.8%). This indicates that the poor prognosis in malignant melanoma of the trunk is due to its tendency to spread tumor cells into more than one lymphatic region.

3.5. Lymph Node Involvement and Survival Rate

As outlined in Figure 6, the survival curves of the cases with lymph node involvement and without, diverge almost significantly. The 5-year survival rate calculated according to the actuarial method is 63.9% ($\pm 8.2\%$) for patients without and 24.7% ($\pm 28.8\%$) for those with metastases. The total survival rate is 48.9% ($\pm 17.8\%$). These data lie within the 5-year survival rates reported by other authors, which range from 41% to 72% [7, 21, 24, 26, 29, 31] depending mainly on case material and therapeutic management but also on the statistical method. However, according to Heite [9], a post-operative observation time of at least 8 years is necessary for the realistic assessment of the survival rates in malignant melanoma.

4. Comment

The data concerning the incidence of regional lymph node metastasis in malignant melanoma are generally based on the *clinical* lymph node findings [1, 4, 14, 20–22, 24–27, 29, 33]. There have been several reports on the *histological* evaluation of lymph node metastases [1, 6, 7, 21, 24, 28], but these deal more often

with therapeutic than with prophylactic lymphadenectomy as a regular measure of treatment: moreover, the modern classification of malignant melanomas according to Clark et al. has not yet been taken into account. This study is supposed to meet the above-mentioned requirements.

In 104 patients who underwent lymphadenectomy, a conspicuously higher percentage of histologically demonstrated lymph node metastases (35.6%) than of clinically suspicious nodes (21.2%) was noted.

When including the case in which lymph nodes appeared insuspicious on palpation, whereas histology later yielded positive results, and vice versa, the discrepancy between histological and clinical findings amounts to 33.7% of our cases. This is mainly due to a large fraction of clinically inapparent lymph node metastases (24%), whereas clinically suspicious nodes with negative histology were found less often (9.7%), but, relatively spoken, clinically suspicious lymph nodes showed a higher incongruence with histology (45.5%) than clinically negative ones (30.5%).

Early spread of tumor cells into regional lymph nodes is considered the most critical event with respect to prognosis. The proven relation of prognosis to clinically suspected regional lymph node involvement [1, 20–22, 24–27, 29, 33] is supported by histology in our cases, the correlation being nearly significant. A conspicuously high incidence of lymph node metastasis was found in malignant melanoma of the trunk and in males, who are known to be preferably affected on this site.

In the assessment of 5-year survival rates of patients with and without lymph node metastasis, our calculation is based on the date of primary tumor operation as the starting point other than the survival rates by Mundth et al. [24] who calculated them from the onset of tumor growth. McBride [3] reported a very high 10 year survival rate (63%) of malignant melanoma patients with lymphadenectomy. This may be due to selection.

Recently, Tonak et al. [31], whose case material includes most of our patients, calculated more favourable 5-year survival times than we do in this study, since they also evaluated cases in early stages (micro-stage 2 and 3) without lymphadenectomy. When comparing prognoses of lymphadenectomized patients only, our data are not less favourable than those published by other authors [1, 6, 7, 21, 24, 28].

Concerning our additional therapeutic management, it could be mentioned that since the end of 1974 our malignant melanoma patients with regional lymph node involvement (patho-stage III) have been treated post-operatively with BCG scarification, some cases with DNCB sensitization as well, in order to stimulate immunological response, but this does not touch the present study.

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Lebenslauf

Am 22. November 1950 wurde ich, Gerhard Aloisius Wutz, als erstes von drei Kindern des Bäckermeisters Franz und seiner Ehefrau Gertraud Wutz, geb. Neft, in Regensburg geboren. Dort besuchte ich von 1957 bis 1961 die Volksschule Reinhausen, von der aus ich in das Albrecht-Altdorfer-Gymnasium in Regensburg übertrat. Am 20. Juni 1970 bestand ich an der bezeichneten Lehranstalt das Abitur.

Nach einem einsemestrigen Studium der Psychologie an der Universität Regensburg begann ich im Sommersemester 1971 an der Friedrich-Alexander-Universität Erlangen-Nürnberg Medizin zu studieren. Die naturwissenschaftliche Vorprüfung legte ich im März 1972, die ärztliche Vorprüfung nach zwei weiteren Semestern im Mai 1973 erfolgreich ab. Die in der Bestallungsordnung für Ärzte ferner geforderten Studienleistungen erbrachte ich im Laufe eines sechssemestrigen klinischen Studiums. Die ärztliche Prüfung bestand ich am 23. Juli 1976 mit dem Urteil "sehr gut".

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